II. Obviousness-type Double Patenting

Claims 1-9 were rejected under the judicially created doctrine of obviousness type double patenting over U.S. Patent No. 5,902,821. (Office Action, pg. 2.) In an effort to advance prosecution, without necessarily agreeing with the rejection, a Terminal Disclaimer over U.S. Patent No. 5,902,821 is being submitted herewith.

III. Rejection under 35 U.S.C. § 103

Claims 1-9 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,308,862 ("Ohlstein") in view of U.S. Patent No. 5,312,828 ("Finkelstein") or U.S. Patent No. 4,888,179 ("Applegren"). (Office Action, pg. 4.) Ohlstein is characterized as teaching that carvedilol is useful in the treatment of congestive heart failure ("CHF"). (*Id.*) The Office recognizes that Ohlstein does not mention decreasing mortality resulting from CHF, but contends that "this is inherent since the primary function, if not the sole purpose of administering a drug to a patient to treat congestive heart failure is to decrease the mortality of the patent in absence of evidence to the contrary." (Office Action, pg. 4.)

Applicants respectfully disagree with the premise of the rejection, and specifically traverse the rejection for at least the following reasons:

> (1) The Office previously considered Ohlstein in view of Finkelstein or Applegren, and found claims directed to methods of administering carvedilol to decrease mortality caused by CHF to be non-obvious over these references;
>
> (2) The rejection presupposes that drugs are administered to CHF patients primarily to decrease mortality, but there is a recognized distinction between (a) treating quality of life or symptoms of CHF and (b) treating CHF mortality; the references and the art as a whole recognized carvedilol for, at most, potential symptomatic treatment;

(3) Surprisingly and unexpectedly, carvedilol substantially decreases CHF mortality, by about 67% according to certain clinical studies, while other beta-blockers actually worsen mortality and the standard therapy, ACE inhibitors, achieve only about 20% mortality reduction; and

(4) Additional claimed features not addressed by the rejection are also not taught or suggested by the reference combinations.

(1) OHLSTEIN ET AL. HAVE BEEN PREVIOUSLY OVERCOME

During the prosecution leading to the U.S. Patent No. 6,760,069 ("the '069 patent"), from which the present reissue is taken, rejections based on Ohlstein in view of Finkelstein or Applegren were successfully traversed. At that time, Applicants provided, among other things, the June 19, 1997, Declaration of Martin Wehling, M.D. (Attached as Exhibit 1.) As explained by Dr. Wehling and discussed further below, clinical testing of other beta-blockers had failed to show any significant decrease in mortality in CHF patients. (Wehling Declaration, ¶6.) Indeed, beta-blockers were contraindicated in patients suffering from CHF because they were known to have undesirable cardiodepressive effects. (Wehling Declaration, ¶¶7-9.) Thus, the use of carvedilol (a beta-blocker) to treat mortality would have been counter to the expectations and experience of one skilled in the art, and would not have been obvious. Further, as evidenced by Dr. Wehling's Declaration, it would have been unexpected for carvedilol to reduce mortality in CHF patients; the mortality reduction of about 67% being particularly unexpected and fulfilling a long-felt need. (*E.g.,* Wehling Declaration ¶¶7, 10, 14, 18.)

Based on the evidence provided in Dr. Wehling's Declaration, including the teaching away from using beta-blockers for CHF patients for mortality reduction, Applicants respectfully submit that the reference combinations fail to render obvious the presently claimed invention. Further, even if the reference combination did establish a

prima facie case of obviousness, the evidence of unexpected results and long-felt need attested to by Dr. Wehling compels a finding of non-obviousness. Additionally, however, Applicants provide below further evidence and reasons why the reference combinations fail to establish a *prima facie* case of obviousness as well as why the use of carvedilol to decrease mortality, as claimed, is objectively non-obvious.

(2) *CARVEDILOL WAS, AT MOST, RECOGNIZED AS A POTENTIAL TREATMENT FOR SYMPTOMS IN CHF PATIENTS*

Concerning the premise of the rejection, that "the primary function ... of administering a drug to a [CHF] patient ... is to decrease mortality," Applicants note that prior to the discoveries forming the basis of the present invention, the only recognized use of carvedilol in CHF patients was for the treatment of the symptoms of CHF, particularly hypertension (high blood pressure). (*See, e.g.,* Affidavit of Dr. Mary Ann Lukas (March 7, 2002) at ¶21-29, Exhibit K of Applicants' December 28, 2004, IDS reference no. 128 ("Applicants' Record, Volume 3 of 7"), attached as Exhibit 2.) The treatment of symptoms, such as high blood pressure, is intended to enhance patient quality of life factors, such as exercise capacity. Symptomatic treatment, however, was not corrected with mortality treatment for CHF patients, and symptomatic treatment does not teach or suggest treatment for mortality. (*Id.* at ¶52; *see also* August 20, 1996, Examiner Interview Summary Record, from the prosecution leading to the '069 patent, attached as Exhibit 3.)

Further, as explained by Dr. Lukas, the prevailing dogma throughout the 1980's and until about 1997 was that beta-blockers were contraindicated for the treatment of CHF patients. (*Id.* at ¶28, 44-45.) This view was supported by early clinical results where patients with angina and CHF worsened or did not improve with beta-blockers.

(Id. at ¶¶28, 44-45, 55 (beta-blocker xamoterol was shown to worsen survival in patients with severe heart failure), 56 (beta-blocker metropolol was shown to improve exercise tolerance and cardiac function, but had no beneficial effect on mortality), 57 (no statistically significant decrease in mortality with beta-blocker bisoprolol). The state of the art is also addressed by the October 1994, CIBIS publication, which states that "a progressively increasing dose of β-blocker in severe heart failure confers functional benefit. . . . However, improvement in survival while on β-blockade remains to be demonstrated." (CIBIS Investigators and Committees, "A Randomized Trial of Beta-Blockade in Heart Failure — The Cardiac Insufficiency Bisoprolol Study (CIBIS)," 90(4) Circulation, Vol. 1765-1773, at 1765 (1994), reference no. 33 in Applicants' December 28, 2004, IDS.)

The known adverse effects of symptomatic treatment drugs, such as anti-hypertensives, in CHF patients reinforced the view that these were contraindicated for CHF patients. (*See, e.g.,* R. DiBianco *et al.*, "A Comparison of Oral Milrinone, Digoxin, and Their Combination in the Treatment of Patients with Chronic Heart Failure," New England J. Med., 320(11), 677-683 (March 1989), reference no. 115, exhibit H, in Applicants' December 28, 2004, IDS.) As clearly stated by DiBianco: "Analysis of mortality from all causes [for moderately severe CHF patients] according to the intention to treat suggested an adverse effect of miliprone . . . . [O]ur data suggests that miliprone may aggravate ventricular arrhythmias." (*Id.* at pg. 1175 (emphasis added); *see also* M. Packer *et al.*, "Effect of Oral Milrinone on Mortality in Severe Chronic Heart Failure," New England J. Med. 325(21), 1468-75 (Nov. 21, 1991), reference no. 115, exhibit I, in Applicants' December 28, 2004, IDS ("Our findings indicate that despite its beneficial hemodynamic actions, long-term therapy with oral

milrinone increase the morbidity and mortality of patients with severe chronic heart failure.").)

In view of this background, the "use" of carvedilol for CHF mentioned in passing by Ohlstein, therefore, is not and cannot be for the treatment of CHF mortality. Rather, Ohlstein can only be understood, in context of one skilled in the art in 1995, as referring to hypertension treatment (*i.e.*, symptomatic treatment) in the presence of CHF.

In fact, looking at just the reference, it is clear that the "treatment" referred to by Ohlstein is the treatment of hypertension (*i.e.*, symptoms) in the presence of CHF, not the treatment of CHF mortality. Specifically, Ohlstein expressly states that the use of carvedilol is "the treatment of mild to moderate hypertension," and goes on to state that the compound *may* have utility in treatment of hypertension in connection with angina or CHF. (Ohlstein, col. 4, ln. 11-15.) Ohlstein specifies that the potential use is for hypertension symptoms (distinct from CHF mortality) based on carvedilol's mechanisms of action. He explains that "[t]he vasodilatory actions of carvedilol results primarily from a_1-adrenoceptor blockade, whereas the b-adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension." (*Id.* at ln. 18-22 (emphasis added).)

Any doubt about Ohlstein's meaning is settled by reference to the journal articles he relies upon as the basis for the cited statement concerning carvedilol. (Ohlstein, col. 4, ln. 22-35.) In particular, Ohlstein cites R. Ruffolo *et al.*, "Carvedilol (Kredex®): A Novel Multiple Action Cardiovascular Agent," *Drugs of Today* 27(7): 465-492 (1991), reference no. 11 in Applicants' December 28, 2004, IDS. According to the Ruffolo *Drugs of Today* article, carvedilol was used to efficaciously treat hypertension. (Ruffolo at 466.) While Ruffolo indicates that trials were then underway to determine the as yet

unknown utility of carvedilol for hypertension in angina and CHF patients, the speculated *potential* use of carvedilol in CHF patients is, however, still the treatment of hypertension — not mortality. (*See, e.g.,* Ruffolo at 484, col. 2, citing Borow *et al.* for treating hypertensive patients with left ventricular dysfunction, and stating that "carvedilol may allow the initiation of [hypertension] therapy in patients to be better tolerated compared to standard [beta] blockers," and expressly providing under the heading "Prescribing Information" that the sole indication is "[t]reatment of essential hypertension.") The question of hypertension treatment in CHF patients using carvedilol was an important one, given the previous findings, discussed above, that beta-blockers had increased mortality in CHF patients, and were thus contraindicated. (*E.g.,* Affidavit of Dr. Mary Ann Lukas (March 7, 2002), ¶¶ 28, 44-45, 55 (beta-blocker xamoterol was shown to worsen survival in patients with severe heart failure), Exhibit 2.)

Although not identical in all respects, the present case has analogies with *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), copy enclosed as Exhibit 4, on appeal from an interference proceeding before the Board of Patent Appeals and Interferences. The count at issue in *Rapoport* reads:

> A method for <u>treatment</u> of sleep apneas comprising administration of a therapeutically effective amount of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment . . . .

254 F.3d at 1056 (emphasis added). On appeal, the Federal Circuit interpreted the preamble phrase "for treatment of sleep apneas" to refer to sleep apnea treatment *per se*, not merely treatment of symptoms associated with sleep apnea. *Id.* at 1059. Specifically, one party in *Rapoport* had argued that the count was anticipated by a reference disclosing the use of the claimed compound for treatment of anxiety and

breathing difficulty, which are symptoms of sleep apnea, even though the reference did not provide for treatment of sleep apnea itself. *Id. at 1061.* The Court rejected that argument. While the reference mentioned the possibility of administering the compound to patients suffering from sleep apnea, "[t]here is no disclosure in the [prior art reference that the compound] is administered to patients suffering from sleep apnea with the intent to cure the underlying condition." *Id.* (emphasis added). Thus, since the claim was interpreted to require that the method be practiced with the intent to achieve the objective stated in the preamble, it was not anticipated by a reference lacking a teaching of treating sleep apnea.[1]

In the present case, therefore, even if Ohlstein is considered to teach or suggest the use of carvedilol to treat symptoms associated with or in the presence of CHF, since Ohlstein (even in view of the secondary references) does not teach or suggest an intended "method of decreasing mortality caused by congestive heart failure in a patient in need thereof," as more specifically set forth in the pending claims, Ohlstein (in view of the secondary references) does not render obvious the claimed subject matter.

Further, it would not have been obvious to administer carvedilol in conjunction with one or more of an ACE diuretic, and digoxin, as more specifically set forth in the claims. This is true at least for the reason that carvedilol was contraindicated for CHF

[1] In *Jansen v. Rexall Sundown, Inc.*, the Federal Circuit reaffirmed the holding of *Rapoport* that a claimed method of treatment is not invalidated by a prior art reference unless that reference provides for practicing the method with the intent to achieve the claimed objective. 342 F.3d 1329, 1333-34 (Fed. Cir. 2003) ("In other words, administering the claimed vitamins in the claimed doses for some purpose other than [the claimed] treating or preventing macrocytic-megaloblastic anemia is not practicing the claimed method....") *See also Glaxo Group Ltd. v. Teva Pharma, Inc.,* 2004 U.S. Dist. LEXIS 16750, at *56-57 (D. Del. 2004).

patients, as noted above, and would not have been used individually much less with one or more additional agents to decrease mortality caused by CHF.

Accordingly, the disclosure of Ohlstein, in view of Applegren or Finkelstein, would not have provided a teaching or suggestion for the use of carvedilol to decrease CHF mortality in a patient in need thereof, as claimed.

(3) CARVEDILOL HAS AN UNEXPECTEDLY HIGH RATE OF MORTALITY REDUCTION

When carvedilol is administered to CHF patients with an intent to treat CHF mortality, the compound provides unexpectedly high rates of mortality reduction. As noted previously, the fact that there is any mortality reduction at all would have been surprising given the prior experience that other beta-blockers increased mortality. Compared to ACE inhibitors, the standard CHF therapy that yields a mortality reduction of only about 20%, the mortality reduction by carvedilol is also surprising and unexpectedly high. (September 25, 1996, Declaration of Neil H. Shusterman, M.D., ¶ 7-8, attached as Exhibit 5.)

Specifically, as discussed above, in the first clinical study (the "GSK carvedilol study") to examine carvedilol's effects on mortality, a dramatic mortality reduction of about 67% was found for all cases mortality in class II-IV CHF patients. A later larger-scale study (the "COPERNICUS Study") focusing on CHF patients with severe heart failure confirmed the surprising ability of carvedilol to reduce mortality in CHF patients, finding a 35% mortality reduction in these severe-heart failure patients.

The fact that mortality reduction by carvedilol was unexpected is well documented in the history and literature both prior and subsequent to the February 8, 1995 foreign priority date for the present reissue application. The "GSK Carvedilol

Study" referenced above was designed and commissioned to study effects of carvedilol in CHF patients on exercise tolerance as measured with various walking tests. (Affidavit of Dr. Mary Ann Lukas (March 7, 2002), ¶ 61 (Exhibit 2).) Given concerns about the use of beta-blockers in CHF patients, an independent Data Safety Monitoring Board ("DSMB") was utilized to monitor the effect of carvedilol on mortality to determine if patient safety was being compromised. (*Id.* at ¶ 62.) However, rather than showing the mortality increase that had been worried about, the GSK Carvedilol Study instead showed a dramatic decrease in the risk of mortality by about 65%. (*Id.* at ¶ 64.)

Based on this dramatic and unexpected decrease in the risk of mortality, the DSMB prematurely terminated the study because it would have been unethical to withhold carvedilol from the placebo-controlled patients. (*Id.* at ¶ 65.) The DSMB specifically recommended that all patients on the placebo arm of the study be offered carvedilol. (*Id.*)

The unexpected success of the GSK Carvedilol Study is documented in various contemporaneous reports. For example, the February 20, 1995 edition of *Chemistry and Industry* (London), No. 4, page 123 contained an article titled "SmithKline Beecham: unexpected success halts drug trial." (Reference no. 41 of Applicants' December 28, 2004, IDS.) As reported in this article, "An independent monitoring group has told [GSK] to halt US trials of [carvedilol] because it's more effective than expected." (*Id.*) The article quotes the DSMB as having stated "to continue administering placebo would be unethical in view of . . . preliminary reviews of the mortality data." (*Id.*)

The published results of the GSK Carvedilol Study further evidence the significant and unexpected mortality reduction that caused the DSMB to prematurely halt the study. (M. Packer *et al.*, "The effect of carvedilol on morbidity and mortality in

patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group," New England J Med. 334(21): 1349-55 (May 23, 1996), reference no. 70 of Applicants' December 28, 2004, IDS.) As reported by Packer, "[r]andomization [of patients for the study] began on April 29, 1994, and the study was stopped early on the recommendation of the [DSMB] of February 3, 1995. This decision was based on the finding of a significant effect of carvedilol on survival — an effect that exceeded all conventional boundaries used to stop clinical trials." (*Id.* at pg. 1350 (citations omitted).) As reported by Packer, the mortality reduction for patients having mild to severe CHF was 65%. (*Id.* at pg. 1350.)

The surprising benefits of carvedilol for mortality reduction were confirmed in a subsequent, larger-scale study, the "COPERNICUS study," focusing on patients with severe CHF. (Affidavit of Dr. Mary Ann Lukas (March 7, 2002), ¶ 69 (Exhibit 2).) The results of this study were published in M. Packer *et al.* "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," 344(22) New England J. Med., 1651-1658 (May 31, 2001) (Reference no. 99 of Applicants' December 28, 2004, IDS).) As reported therein, the only prior large-scale study of using a beta-blocker (bucindolol) in patients with severe heart failure suggested that beta-blockers may adversely affect patients at the highest risk. (*Id.* at pg. 1651.) However, the COPERNICUS study showed that for patients with severe heart failure there was a 35% decrease in the risk of death using carvedilol as compared with placebo. (*Id.*) According to these results, "if physicians treated 1000 patients with severe heart failure similar to that our in [the COPERNICUS study] with carvedilol for one year, approximately 70 premature deaths would be prevented." (*Id.* at 1657.)

Therefore, although Applicants maintain that Ohlstein in view of Finkelstein or Applegren fail to establish a *prima facie* case of obviousness, even if they (or any other reference combination) did so, the evidence of the unexpected results, including the quantitatively large decrease in mortality, compels a finding of non-obviousness.

(4) ADDITIONAL FEATURES NOT TAUGHT OR SUGGESTED

(i) Claim 1

According to amended claim 1, the method comprises "administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months." The references, however, do not teach or suggest the claimed method comprising this maintenance treatment.

For clinical use, Ohlstein provides for administration of carvedilol for the prevention of reocclusion after percutaneous transluminal coronary angioplasty (PTCA) "before, during, and for up to six months post-angioplasty. . . ." (Col. 7, ln. 58-68.) Ohlstein also states that preferred dosages will vary according to factors such as the disease being treated. (Col. 7, ln. 68 - col. 8, ln. 6.) Neither statement, however, is a teaching or suggestion of "administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months," as claimed according to amended claim 1. The secondary references, and Ohlstein in view of the secondary references, also do not teach or suggest the recited administering.

(ii) Claim 8

Claim 8 recites the method according to claim 1, "wherein the daily maintenance dosages and the maintenance period have been shown to statistically decrease the risk

of mortality caused by congestive heart failure." Ohlstein, even in view of the secondary references, also does not teach or suggest daily maintenance dosages or a daily maintenance period shown to statistically decrease the risk of morality caused by CHF, as claimed.

(iii) Claim 9

Claim 9 recites that the patient in need of treatment to decrease the risk of mortality caused by the CHF has class II-IV congestive heart failure. Ohlstein, Finkelstein, and Appelgren lack any disclosure related to treatment based on CHF classification. They necessarily, therefore, lack any teaching or suggestion of treating class II-IV CHF patients, as more specifically recited in claim 9.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. The Examiner is invited to contact Applicants' undersigned representative by telephone at (202) 408-4092 to discuss this case.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 22, 2005

By: _____
Mark J. Feldstein
Reg. No. 46,693

Enclosures:

1 Declaration of Martin Wehling, M.D. (June 19, 1997), from Application No. 08/483,635.

2 Affidavit of Dr. Mary Ann Lukas (March 7, 2002) (associated exhibits can be found at Exhibit K of Applicants' December 28, 2004, IDS reference no. 128 ("Applicants' Record, Volume 3 of 7")).

3 August 20, 1996, Examiner Interview Summary Record from Application No. 08/483,635.

4 *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001).

5 Declaration of Neil H. Shusterman, M.D (September 25, 1996), from Application No. 08/483,635.